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NAME OF PERSON MAILING PAPER OR FEE (TYPE OR PRINT) DIANE W. HALATA

SIGNATURE Diane W. Halata

93 APR 30 PM 7:18

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re : U.S. Patent 4,721,723

Issued : January 26, 1988

To : Roger D. Barnes, et al

For : ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE

APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. 156

Hon. Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

Sir:

The Applicant, Beecham Group p.l.c., of England, represents that it is the Assignee of the entire right, title and interest in and to United States Patent No. 4 ,721,723 (hereinafter, "the Patent"), granted to Beecham Group p.l.c. on January 26, 1988, by virtue of assignments recorded February 13, 1987, Reel 4689, Frame 508.

The Applicant hereby requests an extension of term of the Patent under 35 U.S.C. §156. The following information as required by 37 C.F.R. §1.740 is set forth below:

SC13081 03/08/93 4721723 19-2570 130 377 1,000.00CH

1. The approved product is PAXIL paroxetine hydrochloride and has the chemical name: (-)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine hydrochloride hemihydrate.

2. The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. 355.

3. The approved product received permission for commercial marketing or use under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) on December 29, 1992.

4. The active ingredient in the approved product is paroxetine hydrochloride hemihydrate. The active ingredient has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act or any other U.S. law.

5. This application for extension of patent term under 35 U.S.C. 156 is being submitted within the sixty day period permitted for submission under 37 CFR 1.710(f), the last day for said submission being March 1, 1993.

6. The complete identification of the patent for which an extension is being sought is as follows:

Inventors: Roger D. Barnes, Marian W. Wood-Kaczmar, Alan D. Curzons, Ian R. Lynch, John E. Richardson and Phillip C. Buxton

Patent No.: 4,721,723

Issue Date: January 26, 1988

Date of Expiration: January 26, 2005

7. A copy of the Patent is attached herewith as "Attachment A".

8. A copy of the receipts for the payment of maintenance fees are attached as "Attachment B".

9. The Patent claims, in claims 1-6, the approved product and a method of using and manufacturing the approved product. More specifically, claims 1, 2 and 3 are directed to crystalline paroxetine hydrochloride hemihydrate (claim 1); crystalline paroxetine hydrochloride hemihydrate in substantially pure form (claim 2); and crystalline paroxetine hydrochloride hemihydrate having a specified X-ray diffractogram pattern, IR spectrum and DSC profile. Claim 4 is directed to a process for preparing crystalline paroxetine hydrochloride hemihydrate. Claim 5 is directed to an anti-depressant pharmaceutical composition comprising crystalline paroxetine hydrochloride hemihydrate. Claim 6 is directed to a method of treating depression in mammals which comprises administering crystalline paroxetine hydrochloride hemihydrate.

10. The relevant dates and information pursuant to 35 U.S.C. 156 (g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(a) The Effective Date of the investigational new drug ("IND") application for the approved product was January 22, 1984 , IND Number 23,280;

(b) A New Drug Application ("NDA") for the approved product was submitted on November 29, 1989 as NDA application number: 20-031 .

(c) NDA number 20-031 was approved on December 29, 1992.

11. During the applicable regulatory review period, the applicant diligently undertook to satisfy the requirements of the Federal Food, Drug and Cosmetic Act as applied to the approved product in order to obtain regulatory approval to sell the approved product. Specific activities and the dates applicable to such activities are summarzied in "Attachment C".

12. Applicant is of the opinion that the Patent is eligible for extension under 35 U.S.C. 156.

The length of extension of the term of the Patent requested by Applicant is 702 days, the maximum possible under 35 U.S.C. 156(c)(3). More specifically:

- the review period under 35 U.S.C. 156(g)(1)(B)(i) was from January 22, 1984 (effective date of IND) until November 29, 1989 (NDA submission date), which is about 1,772 days;
- the review period under 35 U.S.C. 156(g)(1)(B)(ii) was from November 29, 1989 (NDA submission date) until December 29, 1992 (NDA approval date), which is 1,125 days;
- under 35 U.S.C. 156(c)(2), in the absence of other statutory limitations, the permitted period of extension would have been one-half the 35 U.S.C. 156(g)(B)(i) period, i.e., about 886 days, plus all of the 35 U.S.C. 156(g)(B)(ii) period, i.e., about 2001 days;
- under 35 U.S.C. 156(g)(6)(A), in the absence of further statutory limitations, the permitted period of extension would have been five (5) years;
- under 35 U.S.C. 156(c)(3), the permitted period of extension is limited to fourteen (14) years from the date of NDA approval, i.e., 14 years from December 29, 1992, which is December 26, 2006;
- the period of time between normal expiration of the Patent and 14 years from the date of NDA approval is 702 days, which is the length of extension requested by Applicant;
- the expiration date of the Patent, extended in accordance with this petition, would be December 29, 2006.

13. Applicant and the undersigned acknowledge a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

14. The prescribed fee of One Thousand Dollars ($1,000) for receiving and acting upon this application of extension, as well as any required additional amounts, is to be charged to applicant's Deposit Account 19-2570 as authorized in the accompanying letter, which is submitted in duplicate.

15. Please direct all inquiries and correspondence relating to this application for patent term extension to:

Edward T. Lentz
Corporate Patents U.S. - UW2220
SmithKline Beecham Corporation
P.O. Box 1539
King of Prussia, Pennsylvania 19406-0939

Telephone (215) 270-5065

16. Attached hereto is a Declaration signed on behalf of Beecham Group p.l.c. which meets the criteria set forth in 37 CFR 1.740(b).

Respectively submitted,

BEECHAM GROUP p.l.c.

By: _____
Edward T. Lentz
Attorney for Applicant
Registration No. 30, 191

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,721,723

Issued: January 26, 1988

To: Roger D. Barnes et al

For: Anti-depressant Crystalline Paroxetine Hydrochloride

93 APR 30 PM 7:18

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

DECLARATION

Sir:

The undersigned Attorney for Beecham Group p.l.c. which is the applicant for extension of patent term under 35 U.S.C. 156 with respect to U.S. Patent No. 4,471,723, hereby declares that:

(1) he is an attorney authorized to practice before the U.S. Patent and Trademark Office and that he has general authority from the owner to act on behalf of the owner in patent matters as demonstrated by the attached Power of Attorney;

(2) he has reviewed and understands the contents of the application being submitted pursuant to 35 U.S.C. 156 and the guidelines for extension of patent term under 37 CFR 1.740;

(3) he believes the patent is eligible for extension pursuant to 35 U.S.C. 156 and the guidelines for extension of patent term under 37 CFR 1.710;

(4) he believes an extension of the length claimed is fully justified under 35 U.S.C. 156 and the applicable regulations; and

(5) he believes the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 35 U.S.C. 156 and the guidelines for extension of patent term under 37 CFR 1.720.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Date: February 23, 1993

Edward T. Lentz
Registration No. 30,191

n:\et\decl.doc

POWER OF ATTORNEY

The undersigned Beecham Group p.l.c., formerly Beecham Group Limited, a corporation of England hereby authorizes in the name and on behalf of Beecham Group p.l.c., Edward T. Lentz, a patent attorney registered with the U.S. Patent and Trademark Office, Registration No. 30,191 whose business address is SmithKline Beecham Corporation, Corporate Patents - U.S., UW2220, P.O. Box 1539, King of Prussia, Pa. 19406-0939, USA to act on behalf of Beecham Group p.l.c. in all patent matters including the power to execute (or revoke) powers of attorney, disclaimers, patent term extensions, concessions of priority, abandonments, assents to filing reissue applications, petitions to make special, applications to correct inventorship, patent assignments, pleadings, interrogatories, oppositions, affidavits of use, and petitions for reexamination, and to execute all other papers and take all such actions as he may deem necessary or appropriate in order to file, prosecute, abandon, terminate, extend or transfer applications for patents and other industrial property rights in the United States and countries foreign thereto, and to defend, assert, and maintain such property rights in full force and effect.

Executed as of the 17th day of February, 1993.

BEECHAM GROUP p.l.c.

David Roberts
As Attorney for and on behalf of
the said Beecham Group p.l.c.

DER

Attachment A

United States Patent [19]

Barnes et al.

[11] Patent Number: 4,721,723

[45] Date of Patent: Jan. 26, 1988

[54] ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE HEMIHYDRATE

[75] Inventors: Roger D. Barnes, Betchworth; Marian W. Wood-Kaczmar, Harlow; Alan D. Curzons, Worthing; Ian R. Lynch, Epsom; John E. Richardson, Harlow; Philip C. Buxton, Epsom, all of England

[73] Assignee: Beecham Group p.l.c., Brentford, England

[21] Appl. No.: 922,530

[22] Filed: Oct. 23, 1986

[30] Foreign Application Priority Data

Oct. 25, 1985 [GB] United Kingdom 8526407
Oct. 25, 1985 [GB] United Kingdom 8526408

[51] Int. Cl.[4] A61K 31/445; C07D 405/12
[52] U.S. Cl. 514/321; 546/197
[58] Field of Search 546/197; 514/321

[56] References Cited

U.S. PATENT DOCUMENTS

4,007,196 2/1977 Christensen 546/197

OTHER PUBLICATIONS

Chemical Abstracts, 95:54664z (1981) [Goethert, M., et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1980, 313(1), 21-6].

J. B. Lassen, *Psychopharmacology*, 57, pp. 151-153 (1978).

J. B. Lassen, *European J. Pharmacol., 47, pp. 351-358 (1978).*

J. Lund et al., *Acta Pharmacol. et Toxicol.*, 44, pp. 289-295 (1979).

J. B. Lassen, et al., *Psychopharmacology*, 68, pp. 229-233 (1980).

Primary Examiner—Richard A. Schwartz
Attorney, Agent, or Firm—James F. Haley, Jr.; Alan M. Gordon

[57] ABSTRACT

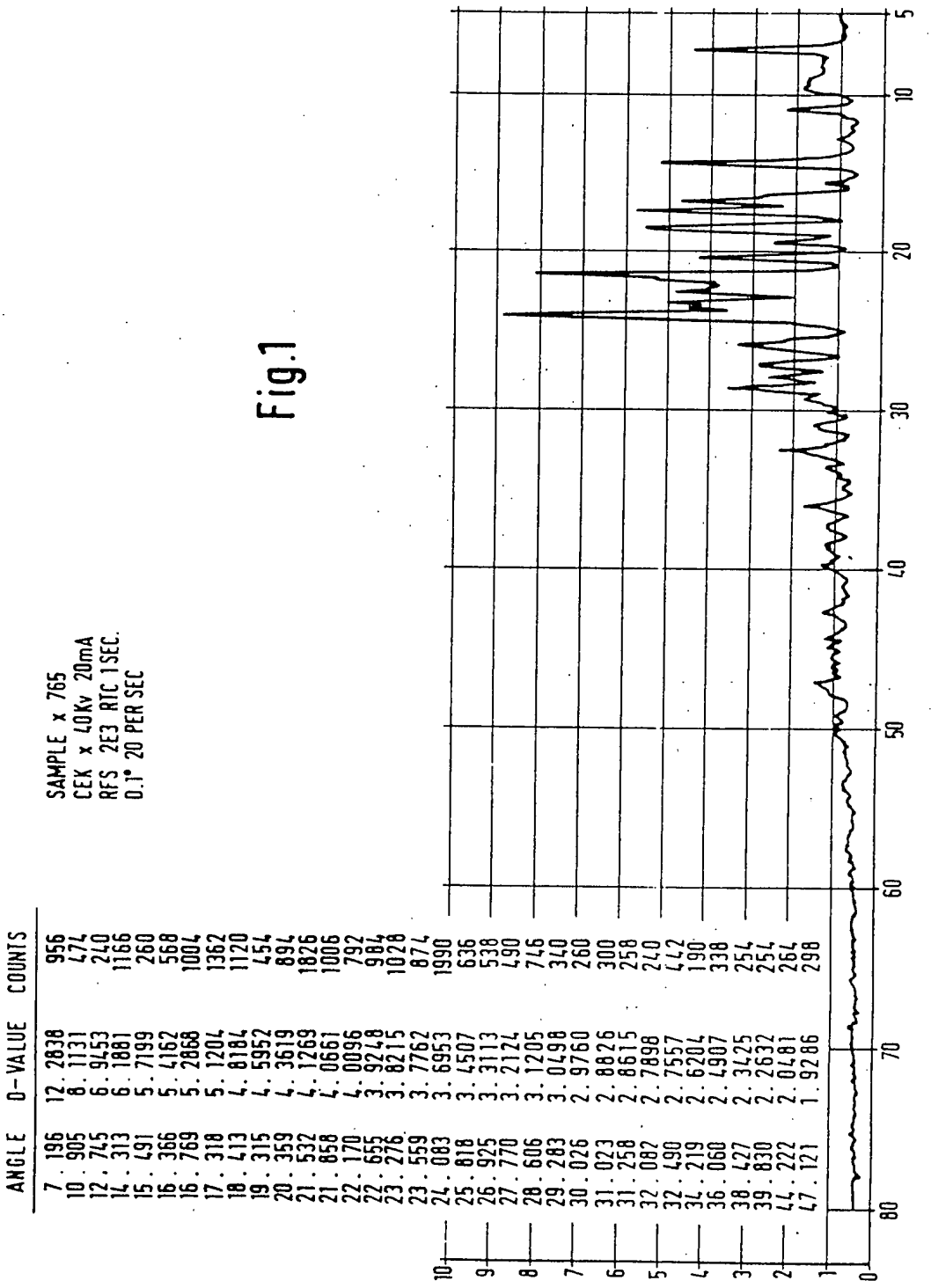
The invention provides crystalline paroxetine hydrochloride hemihydrate, processes for its preparation, compositions containing the same and its therapeutic use as an anti-depressant.

6 Claims, 3 Drawing Figures

ATTACHMENT A

U.S. PATENT NO. 4,721,723

Fig.1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32.490 2.7557 442
34.219 2.6204 190
36.060 2.4907 338
38.427 2.3425 254
39.830 2.2632 254
44.222 2.0481 264
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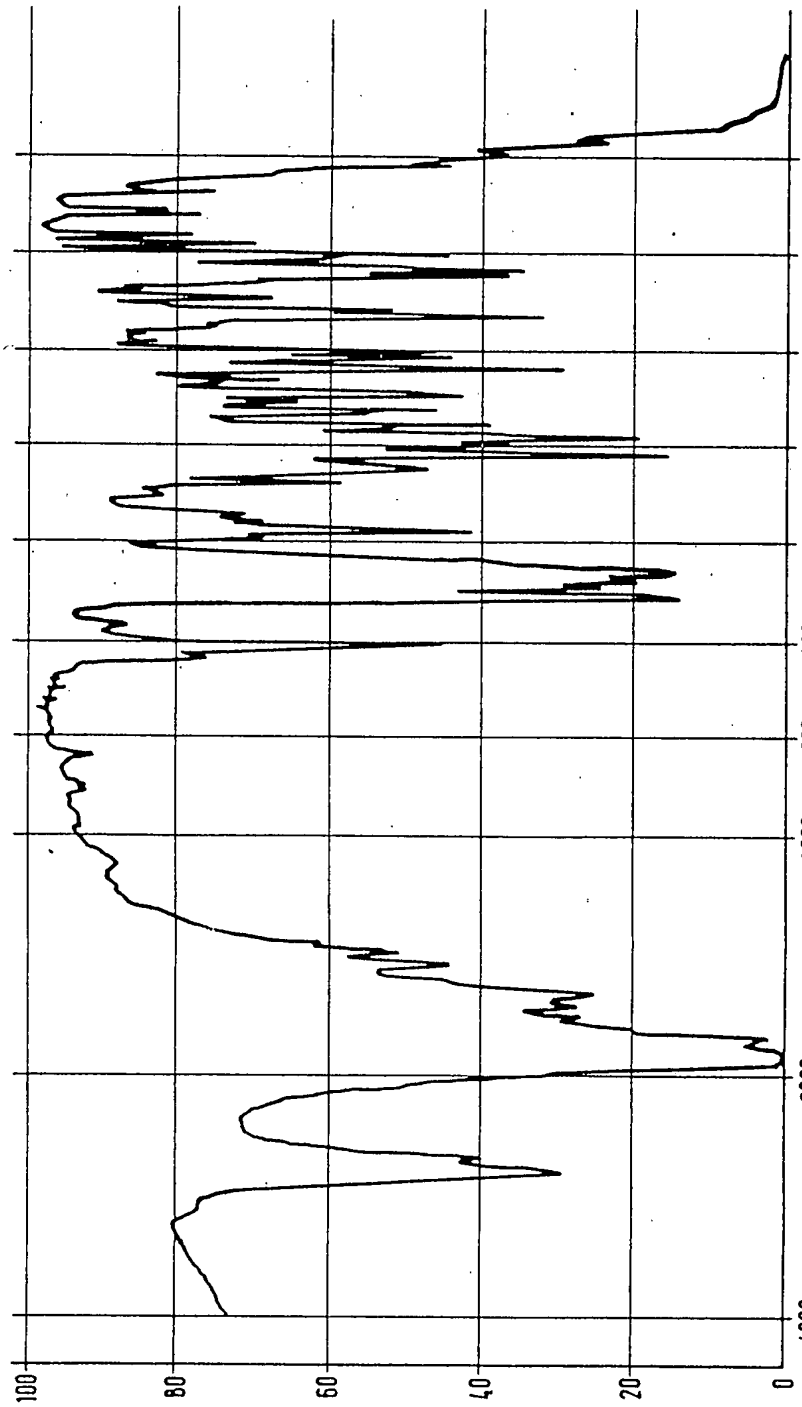
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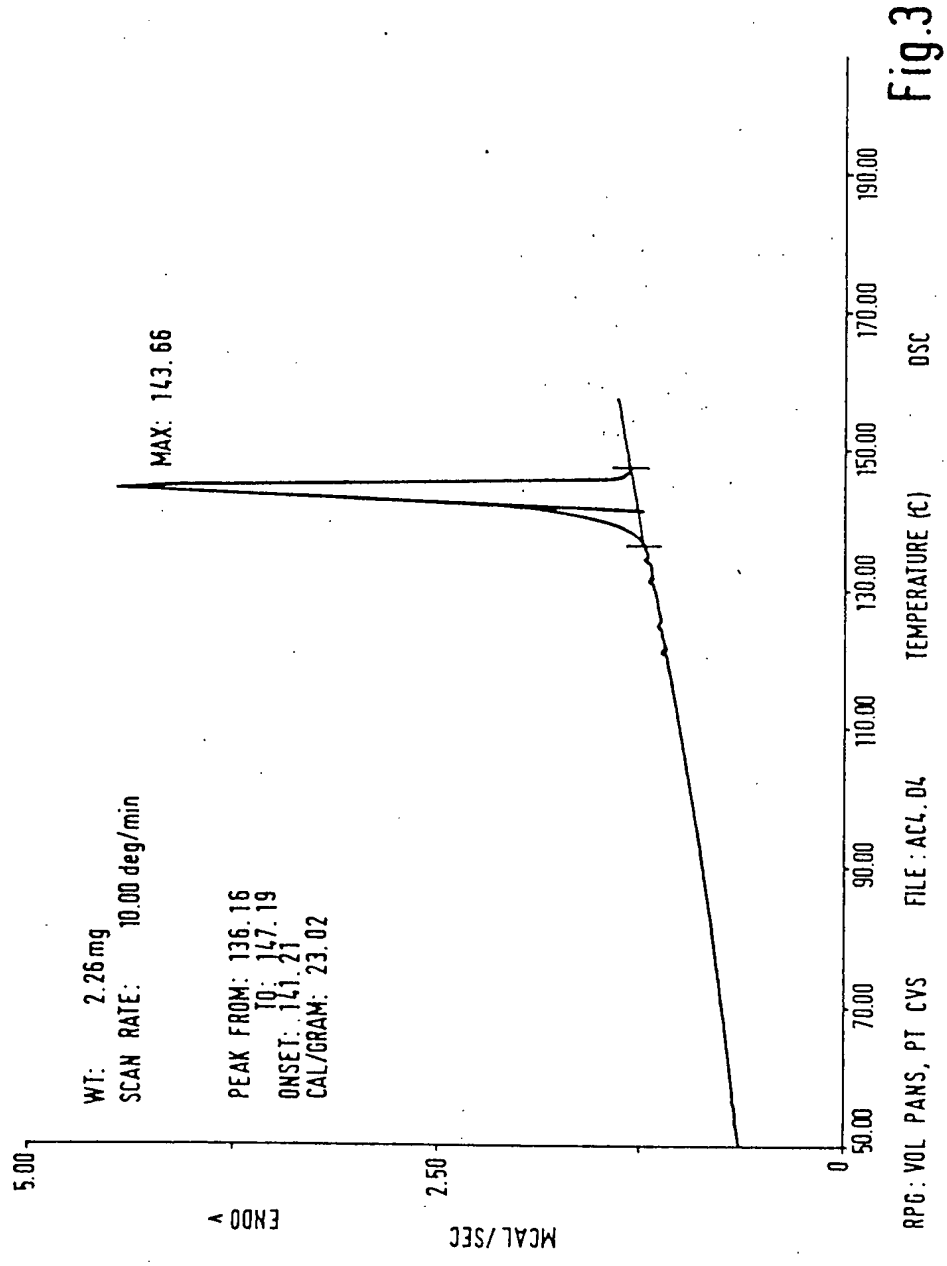
SCAN 12 MINS
SLIT N

Fig.2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PEAK FROM: 136.16
TO: 147.19
ONSET: 141.21
CAL/GRAM: 23.02
5.00
2.50
0
ENDO ▼
MCAL/SEC
50.00
70.00
90.00
110.00
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150.00
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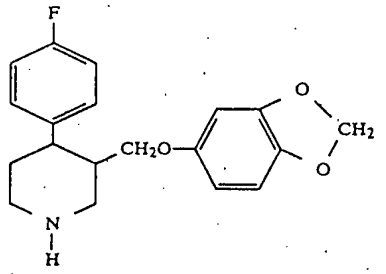
TEMPERATURE (C)
DSC
RPG: VOL PANS, PT CVS
FILE: ACL.04

Fig.3

ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE HEMIHYDRATE

This invention relates to crystalline paroxetine hydrochloride, its preparation and its use as a therapeutic agent.

U.S. Pat. No. 4,007,196 discloses a class of compounds that are inhibitors of 5-hydroxytryptamine (5HT) uptake and thus of therapeutic use as anti-depressants. In Example 2 of the U.S. patent there is described the preparation of (−)-trans-4-(4'-fluorophenyl) 3-(3'4'-methylenedioxyphenoxymethyl)-piperidine of formula A:



(A)

In this specification the compound of formula A is referred to by its generic name of paroxetine.

Because of its basicity, it is preferred that paroxetine is used as a therapeutic agent in the form of an acid addition salt. In Example 2 of U.S. Pat. No. 4,007,196, paroxetine is obtained as the free base and then converted to its maleic acid salt.

The acetate salt of paroxetine has been used in most of the published experimental trials [for example, *Psychopharmacology*, 57, 151–153 (1978); *ibid.* 68, 229–233 (1980); and *European Journal of Pharmacology*, 47 (1978) 351–358]. There has also been limited use of the hydrochloride salt (in aqueous solution) [*Acta. Pharmacol. et Toxicol.* 1979, 44, 289–295]. However, the preparation of paroxetine hydrochloride has not been described in the literature.

In general, the hydrochloride salt of a basic compound is preferred for therapeutic use because of its physiological acceptability.

However for commercial use it is also important that the solid product should have good handling qualities.

We have found that amorphous paroxetine hydrochloride is a hygroscopic solid of poor handling qualities.

It has now been discovered that paroxetine hydrochloride can be produced in crystalline form in a manner reproducible on a commercial scale.

The present invention provides crystalline paroxetine hydrochloride hemihydrate as a novel material, in particular in pharmaceutically acceptable form.

Paroxetine hydrochloride hemihydrate is stable and non-hygroscopic. It is characterised by an X-ray powder diffractogram as shown in the accompanying FIG. 1. A typical Nujol infra-red spectrum (FIG. 2) and DSC profile (prepared using a 2.26 mg sample in a sealed container (FIG. 3) is also shown. Under extreme dessication conditions the bound water may be removed to give an anhydrous form, but on rehydration it rapidly reforms the hemihydrate.

The present invention also provides a process for producing crystalline paroxetine hydrochloride hemihydrate which comprises forming a solution of paroxetine hydrochloride and precipitating the crystalline form from solution.

The solution may be formed by dissolution of preformed paroxetine hydrochloride or by forming the hydrochloride in situ. The hydrochloride may be formed from a solution of paroxetine free base or a salt other than the hydrochloride by contacting it with hydrogen chloride.

For example a solution of hydrogen chloride, for example concentrated hydrochloric acid or an organic solvent saturated with hydrogen chloride may be added to a solution of paroxetine salt. Alternatively hydrogen chloride gas may be passed through the paroxetine (salt) solution.

Paroxetine base may be prepared by the procedure disclosed in U.S. Pat. No. 4,007,196. The U.S. Patent also gives procedures for preparing salts of paroxetine with various organic acids.

Typically, paroxetine hydrochloride may be obtained from an organic solution e.g. in toluene, of the free base by adding an appropiate amount of aqueous HCl.

In a procedure using a salt, paroxetine hydrochloride may be produced from a paroxetine C_{1-5} carboxylate such as the acetate. The acetate may be obtained by reaction of acetic acid and paroxetine base in a non-polar solvent, such as diethyl ether or isopropyl ether. Alternatively it may be obtained from an aqueous solution obtained by extraction from a water-immiscible solvent e.g. toluene, ethyl acetate, by the addition of water and an appropriate amount of acetic acid.

Before conversion to the hydrochloride or crystallisation it may be desirable to remove impurities, since it has been found that some impurities may act as crystallisation inhibitors. However, the hemihydrate can even be obtained from relatively impure starting material, by means of seeding.

Paroxetine hydrochloride may be obtained as a crystalline hemihydrate by crystallization after addition of an aqueous solution of hydrochloric acid to a solution of paroxetine free base in water immiscible solvents e.g. toluene, or by crystallisation from water miscible solvents which do not form a solvate (e.g. IMS) after adding aqueous hydrochloric acid to a solution of the free base or by crystallising or recrystallising paroxetine hydrochloride from a solvent system containing water e.g. IMS/water. Alternatively the hydrochloride hemihydrate can be produced via another paroxetine salt by the addition of hydrochloric acid to an aqueous solution of the salt e.g. acetate.

In a preferred aspect, this invention provides paroxetine hydrochloride hemihydrate which is substantially pure.

The hemihydrate can be obtained by crystallisation from a range of solvents, although seeding may be necessary in some instances, after addition of aqueous HCl to a solution of the free base or another salt. Solvents which have been found suitable are toluene, water, IMS, lower alcohols such as ethanol and isopropanol and ethyl acetate. The same solvent range may be used for recrystallizatation.

In a particular aspect of the invention, paroxetine free base is synthesised in a particularly pure form which is especially suitable for use in the preparation of the crystalline paroxetine hydrochloride hemihydrate of the invention, even without seeding.

In the above mentioned U.S. Pat. No. 4,007,196, for the preparation of paroxetine (Examples 1 and 2), an N-methyl compound is reacted with phenyl chloroformate and the resultant compound is hydrolysed with potassium hydroxide.

One disadvantage of this process is that the solvent used during the hydrolysis step (methyl cellosolve) leads to the production of unwanted transesterification by-products.

We have now discovered that the purity of the final product can be improved by using a different solvent during the hydrolysis step, such as toluene. A further advantage is that the temperature at which the hydrolysis is carried out can thus be reduced, owing to the reduction in boiling point of the solvent used.

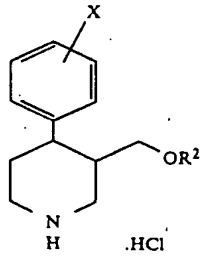
The pure paroxetine free base thus obtained can then be used for the preparation of crystalline paroxetine hydrochloride hemihydrate as set out above.

In a further aspect of the invention, crystalline paroxetine hydrochloride hemihydrate can be obtained by compressing crystalline paroxetine hydrochloride anhydrate.

In a still further particular aspect of the invention, paroxetine is synthesised directly as its hydrochloride salt, followed by crystallization as set out above.

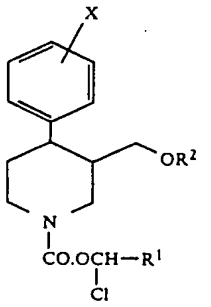
We have discovered a new process for the preparation of paroxetine and related compounds by a de-acylation procedure which advantageously provides the desirable hydrochloride salt directly.

Accordingly, the present invention provides a process for the preparation of a compound of formula I



I

in which R^2 represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, C_{1-6} alkylthio, C_{1-6} alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl, and X represents hydrogen, alkyl having 1–4 carbon atoms, C_{1-6} alkoxy, C_{1-6} trifluoroalkyl (preferably, trifluoromethyl), hydroxy, halogen, methylthio, or aryl(C_{1-6})alkyloxy (e.g., phenyl(C_{1-6})alkyloxy and benzyl(C_{1-6})alkyloxy) by de-acylating a compound of formula II

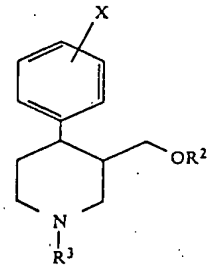


II

in which R^1 is a C_{1-6} alkyl group and X is as defined for formula I.

The de-acylation may be achieved by heating the compound of formula II in a lower alcohol e.g. methanol. Preferably R^1 is a methyl group.

The de-acylation is advantageously carried out as the final step of a procedure for de-alkylating a compound of formula III

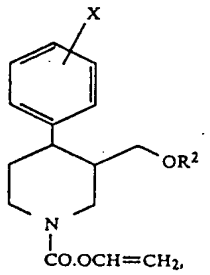


III

in which R^3 is a C_{1-6} alkyl group and X is as defined for formula I.

The replacement of R^3 by R^1.CHClO.CO to convert the compound of formula III to the compound of formula II may be achieved by reacting the compound of formula III with α-chloro-ethyl chloroformate in a solvent such as dichloroethane or toluene.

Alternatively, the compound of formula III may be reacted with vinyl chloroformate in a solvent such as methylene dichloride or toluene to obtain the intermediate of formula IV



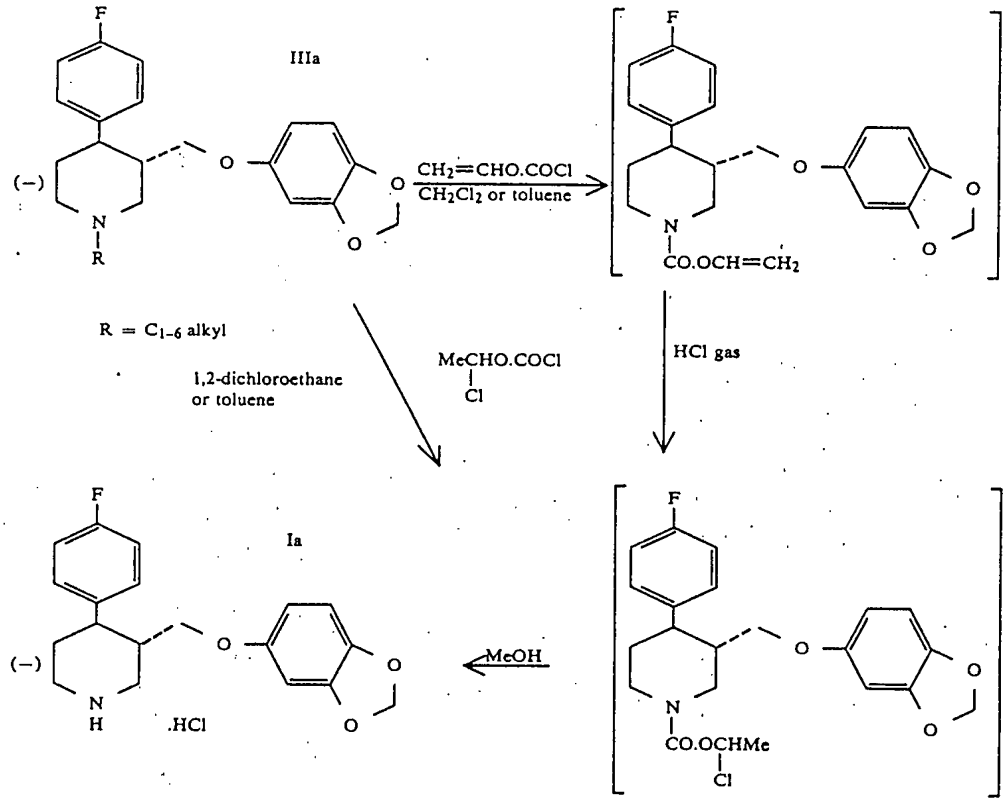
IV

wherein X and R^2 are as defined for formula I, which is then treated with HCl, preferably by passing HCl gas through the solution to obtain the compound of formula II.

An advantageous feature of this process is that the conversion of the compound of formula III into the compound of formula I can be carried out as a 'one-pot' process without isolating the intermediate of formula II or the intermediate of formula IV if the alternative route is followed.

The compounds of formula III may be prepared by the procedures set out in U.S. Pat. No. 4,007,196.

Advantageously, the process is used for the de-alkylation of a compound of formula IIIa to obtain paroxetine hyrochloride of formula Ia. This procedure is illustrated in the following reaction scheme.



The intermediates having the general formulae II and IV given above are novel compounds. They form part of the present invention, together with the processes for their preparation described herein. Compounds of formula I, which include paroxetine hydrochloride, are useful as antidepressants, as disclosed in U.S. Pat. No. 4,007,196, the disclosure of which is hereby incorporated herein by reference. In its preferred aspect the present invention provides paroxetine hydrochloride hemihydrate in pharmaceutically acceptable form.

The present invention also provides a pharmaceutical composition comprising crystalline paroxetine hydrochloride hemihydrate and a pharmaceutically acceptable carrier.

The compositions of this invention are usually adapted for oral administration, but formulations for dissolution for parenteral administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200 mg, more usually from 5 to 100 mg, for example 10 to 50 mg such as 12.5, 15, 20, 25 or 30 mg. Such composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg.

Preferred unit dosage forms include tablets or capsules.

The composition of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or a preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for clinically used anti-depressant agents.

The invention also provides a method of treatment of depression in mammals including humans which method comprises administering an effective amount of pharmaceutically acceptable crystalline paroxetine hydrochloride hemihydrate.

The invention further provides pharmaceutically acceptable crystalline paroxetine hydrochloride hemihydrate for use in the treatment of depression.

The following Examples illustrate the invention. Examples 4 and 5 show the route formula III-IV-II-I, while Examples 6 and 7 show the route formula III-II-I. Temperatures are in ° C.

EXAMPLE 1

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-N-phenoxycarbonylpiperidine (18.5gms) was dissolved in toluene(275 mls). Potassium hydroxide (15.7 gms) was added. The mixture was refluxed for 2 hours with good agitation. The slurry was then cooled to 20° C. and the toluene washed once with water (275 mls).

To a solution of 13.5 g Paroxetine free base in toluene(300 ml) was added a small excess of either concentrated hydrochloric acid(5.2 ml)or dilute hyirochloric acid (150 mls of 0.35N)

The slurry was stirred at ambient temperature for 2 hours. The product was washed with toluene/water(25

ml 1:1 mixture) and dried at 50° C. to give paroxetine hydrochloride as the hemihydrate ($\frac{1}{2}H_2O$) containing 2.5% H_2O with m.p. 128°–133° C., and IR consistent with that shown in FIG. 2.

EXAMPLE 2

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

To a solution of paroxetine free base obtained as described in Example 1 [23.5g] in toluene (ca.500 ml) was added 300 ml water. Acetic acid was added (6.4 g) and after 15 minutes stirring the lower aqueous layer containing paroxetine acetate was separated.

The aqueous layer was clarified by filtration through celite. Concentrated hydrochloric acid (15. Oml) was then added at ambient temperatures in the presence of paroxetine hydrochloride seed obtained as in Example 1 and the precipitated product stirred for 1 hour at ambient and then 2 hours at 0°–5° C.

The product was filtered, washed with water (2x40 ml)and dried at 50° C. to give paroxetine hydrochloride hemihydrate containing 2.6% H_2O and consistent IR.

EXAMPLE 3

Recrystallisation of Paroxetine hydrochloride to give the hemihydrate

(a) 0.50 g Paroxetine hydrochloride was recrystallised from 2.5 ml IMS (industrial methylated spirit) by dissolving at ca 60°–70° C. and cooling slowly to 20° C. then to 5° C. After seeding with crystals obtained as in Example 1, crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

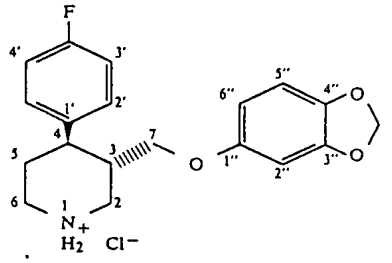
(b) 0.75 gm Paroxetine hydrochloride was recrystallised from 5. Oml water by dissolving at ca. 70° C. and cooling slowly to 20° C. After seeding with crystals obtained as in Example 1, crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

EXAMPLE 4

(−-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-dioxyphenoxymethyl)-piperidine hydrochloride

Vinyl chloroformate (6.42 ml) was dissolved in 2 ml dry methylene dichloride. The solution was cooled to 0° and the reaction flask purged with nitrogen. A solution of (−)-trans-4-(4'-fluorophenyl)-3-(3',4'methylenedioxy-phenoxy) methyl-N-methyl- piperidine (20 g) in 52 ml of dry methylene dichloride was added to the vinyl chloroformate solution over 30 minutes keeping the temperature below 0° . The mixture was allowed to warm to ambient temperature and stirred for 3 hours. The solution was then heated to reflux at 35° for a further 1 hour and cooled to −20° . Dry hydrogen chloride gas was bubbled into the solution for about 1 hour and the mixture allowed to stir at ambient temperature for 1 hour. Methanol (50 ml) was added to the solution and the mixture heated under reflux for 1 hour, followed by addition of charcoal (4.5 g) to the hot solution. Charcoal was filtered off after 10 minutes and the solvents removed in vacuo to give the crude product (21.4 g). The solid was dissolved in isoprOpyl alcohol (140 ml) and the solution filtered. The clear filtrate was cooled to 0° and seeded with crystals obtained as in Example 1 to allow the product to crystallise. After several hours at 0° the white solid was filtered off and the product slurried in water (30 ml), filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (15.8 g, 74.1%).

^1H—n.m.r. (270 MHz, DMSO—d_6)



δ	Multiplicity	Assignment	
9.50	s, br, exch.	NH_2^+	2H
7.27	dd, $^4J_{HF}$ = 6Hz	2'	2H
7.17	dd, $^3J_{HF}$ = 9Hz	3'	2H
6.75	d	5''	1H
6.50	d	2''	1H
6.20	dd	6''	1H
5.94	s	O—CH_2—O	2H
3.61	dd	7	2H
3.53	dd		
3.50	m	2 eq	1H
3.39	d, br	6 eq	1H
3.03	ddd	6 ax	1H
2.97	dd	2 ax	1H
2.90	ddd	4	1H
2.58	m	3	1H
2.10	ddd	5 ax	1H
1.85	d, br	5 eq	1H

EXAMPLE 5

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl-piperidine hydrochloride

The reaction described in Example 4 was repeated substituting 100 ml of sodium dried toluene for 52 ml of dry methylene chloride. (−)-trans-4-(4'-Fluorophenyl)-(3+,4'-methylenedioxyphenoxymethyl)-N-methylpiperidine (20 g) was converted to 16.5 g of the hydrochloride salt as the hemihydrate in a yield of 77.4%.

The ^1H-n.m.r. spectrum was identical to that of the Example 4 product.

EXAMPLE 6

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'methylenedioxyphenoxymethyl)-piperidine hydrochloride

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-N-methylpiperidine (10 g) and N,N,N',N'-tetramethyl-1,8-naphthalenediamine (0.3 g) were dissolved in 40 ml of dry 1,2-dichlorethane (EDC) and the solution cooled to −3° . α-Chloroethyl chloroformate (3.22 ml) in 5 ml of dry EDC was added to the cold solution over 15 minutes. The mixture was stirred for 20 hours at ambient temperature and then heated to reflux for 2 hours. Methanol (15 ml) was added to the solution and the mixture was refluxed for a further 2 hours. The mixture was washed with 20 ml of 1N hydrochloric acid and the phases were allowed to separate. The organic layer was evaporated to dryness and the residue was dissolved in isopropyl alcohol (60 ml). The hot solution was treated with charcoal (2 g) and alumina (1.5 g), stirred for 5 minutes and filtered hot. The clear solution was seeded with crystals obtained as in Example 1 and cooled to 0° for 18 hours. The white crystal-

line solid was filtered off and the wet product slurried in water (20 ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (7.9 g, 74.1%).

The ^{1}H-n.m.r. spectrum was the same as that of the Example 4 product.

EXAMPLE 7

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-N-methylpiperidine (10 g) was dissolved in 45 ml of sodium dried toluene and the solution cooled to 5° . α-Chloroethyl chloroformate (3.22 ml) in 5 ml of dry toluene was added to the cold solution over 15 minutes. The mixture was stirred for 18 hours and methanol (15 ml) was added to the mixture. The solution was stirred for 12 hours at ambient temperature. The solvent was then distilled off in vacuo and the residue dissolved in hot isopropyl alcohol (60 ml). The hot solution was treated with charcoal (2 g) and alumina (1.5 g), stirred for 5 minutes, filtered, seeded with crystals obtained as in Example 1 and cooled to 0° for 18 hours. The white crystalline solid was filtered off, washed with a little isopropyl alcohol and the solid slurried in water (20 ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (9.8 g, 92%).

The ^{1}H-n.m.r. spectrum was identical to that of the Example 4 product.

EXAMPLE 8

(−)-trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride (paroxetine hydrochloride)

Crude (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine (0.341 kg) is dissolved in diethyl ether (3.5 liters) and stirred with aluminium oxide (ca. 0.3 kg) for about 3 hours. Charcoal (15 g) and filter aid (celite, 15 g) are added and the mixture filtered through a layer of aluminium oxide, the filtered solids being washed with more ether. To the combined ether solutions is added a mixture of acetic acid (66 ml) and ether whereupon the acetate of (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine crystallises and is filtered off, washed with ether and dried.

The acetate salt is dissolved in isopropanol (2.4 liters) and treated with a mixture of concentrated hydrochloric acid (75 ml) and more isopropanol. After standing at about 0° C. for about 16 hours, the crystals of the hydrochloride salt containing isopropanol (needles) are filtered off and dried. The salt is stirred in distilled water (0.5 liters) for about 20 minutes, filtered off and dried, giving (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine hydrochloride anhydrate (platelets m.p. 118° C.). IR(Nujol Mull) ν890,1200, 1490, 3400, 3640 cm^{-1}.

Samples of the anhydrate were compressed at approximately 750 MNm^{-2} and approximately 375 MNm^{-2} for periods of about 2 minutes. The former underwent 45% conversion to the hemihydrate, whilst the latter remained unchanged.

Upon reexamining the samples after storage for several days, it was seen that the former sample had undergone complete conversion to the hemihydrate, whilst the latter sample had undergone about 50% conversion.

After a further week, the conversion of the latter sample was almost complete.

We claim:

1. Crystalline paroxetine hydrochloride hemihydrate.

2. Crystalline paroxetine hydrochloride hemihydrate in substantially pure form.

3. Crystalline paroxetine hydrochloride hemihydrate, having substantially the same X-ray diffractogram as set out in FIG. 1, substantially the same IR spectrum, in a Nujol mull, as set out in FIG. 2, and substantially the same DSC profile as set out in FIG. 3.

4. A process for the preparation of crystalline paroxetine hydrochloride hemihydrate, which process comprises forming a solution of paroxetine hydrochloride and crystallizing said hemihydrate from solution by precipitation or recrystallization.

5. An anti-depressant pharmaceutical composition comprising an effective anti-depressant amount of crystalline paroxetine hydrochloride hemihydrate and a pharmaceutically acceptable carrier.

6. A method of treatment of depression in mammals, which method comprises administering an effective amount of crystalline paroxetine hydrochloride hemihydrate.

* * * * *

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Country	Patent No.	Due Date	Annuity	Your Reference Patentee
USA (FULL FEES)	4721723	JUL.26	04	BHD B1942 CRYST.PAROXETINE HCL BEECHAM GROUP -922530-230CT86

ATTACHMENT B

RECEIPTS FOR THE PAYMENT OF MAINTENANCE FEES.

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	Patent no.	Due Date	Year	Patentee	Serial No.	Filing Date	Fee $
USA (FULL FEES)	4721717	JUL.26	4	BOEHRINGER MANN	-760128	-29JUL85	830.00
USA (FULL FEES)	• 4721720	JUL.26	4	BEECHAM GROUP	-838904	-12MAR86	830.00
USA (FULL FEES)	• 4721723	JUL.26	4	BEECHAM GROUP	-922530	-23OCT86	830.00
USA (FULL FEES)	• 4721732	JUL.26	4	SCIMAT LTD	-858484	-30APR86	830.00
USA (FULL FEES)	4721734	JUL.26	4	MERCK PATENT	-646225	-31AUG84	830.00
USA (FULL FEES)	• 4721740	JUL.26	4	BRIDGESTONE CORP	-883225	-08JUL86	830.00
USA (FULL FEES)	• 4721744	JUL.26	4	SUMITOMO CHEM.CO	-846050	-31MAR86	830.00
USA (FULL FEES)	4721749	JUL.26	4	POLYSAR LTD	-912508	-29SEP86	830.00
USA (FULL FEES)	4721754	JUL.26	4	ATOCHEM	-888653	-23JUL86	830.00
USA (FULL FEES)	4721761	JUL.26	4	SUMITOMO CHEM.CO	-892030	-25NOV85	830.00

REPRESENTATIVE PARTNERS: B.S. GOLDSMITH, W.P. McCALLUM, A. MASSEY, R. PRUTTON, C.R. HAIGH, D.M. FOSTER, G.E. SPENCER, SHEILA F. LESLEY, J.N. LEACH, P.M. GORE, W.J.A. BEESTON, N.R. JENNINGS, S.J. COLGAN, P.D.J. WRIGHT, M.J. BRUNNER, S. SMITH, O.J.R. ALLEN, D.G. GELDARD, P. COXON, J. TERRY, R.B. THOMSON. A FULL LIST OF PARTNERS IS AVAILABLE AT OUR OFFICE ADDRESS: C.P.A.

ATTACHMENT B

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ATTACHMENT C

APPLICANT'S ACTIVITIES DURING REGULATORY REVIEW PERIOD.

December 21, 1983	Notice of Claimed Investigational Exemption for Paroxetine submitted. PROPOSED PROTOCOL
January 11, 1984	Agency, by letter, indicates that they received our submission on 12-22-83. IND #23,280 is assigned.
January ~~30~~ 27, 1984	Agency advising that studies could commence; however, a letter is to follow this telephone conversation outlining specific caveats.
February 2, 1984	Revisions for proposed protocol of 12-21-83 submitted.
February 16, 1984	Agency commenting on our 12-21-83 submission.
February 21, 1984	Filed Protocol No. Parol-01 - A Phase II Controlled Double-Blind Study of Paroxetine In Depressed Outpatients. Investigator J. B. Cohn.
March 7, 1984	Amendment to Paroxetine to up-date Volume 1.1.
April 18, 1984	Advising Agency that we have received their letter of 2-16-84.
April 27, 1984	Updated patient consent form to be used by Dr. J. B. Cohn in his study for Parol-01.
October 5, 1984	Amendment to Protocol No. Parol-01 A Phase II Controlled Double-Blind Study in Depressed Outpatients. Investigator Dr. Jay B. Cohn.
December 18, 1984	Submitted Annual Progress Report covering Dec. 1983-Dec. 1984.
April 17, 1985	MEP - Amendment to up-date Section 2-5 and also include 4 Protocols.
April 25, 1985	Notice of Claimed Investigational Exemption submitted to include study to include Protocol No. PAR-05, principal investigators will be James B. Bremner, M.D., and John P. Feighner, M.D.
April 26, 1985	Notice of Claimed Investigational Exemption submitted to include study for PAR-03 and PAR-04, principal investigator Joseph Mendels, M.D.

April 26, 1985	Notice of Claimed Investigational Exemption submitted to include Protocol No. PAR-09, principal investigator to be Earl D. Hearst, M.D.
May 2, 1985	Amended Notice of Claimed Investigational Exemption to include study under Protocol PAR-02.
May 6, 1985	Amended Notice of Claimed Investigational Exemption to include study under Protocol PAR-04.
May 31, 1985	Submitted amendment to update Sections 6(a) and 6(b) of original submission.
June 12, 1985	Submitted revision to provide for inclusion of one additional investigator for clinical study under Protocol No. PAR-03 and extension study under Protocol No. PAR-04.
June 18, 1985	Submitted revision to provide for two additional physicians for a clinical study under Protocol Nos. PAR-03 and PAR-04.
July 1, 1985	Submitted revision to provide for an additional physican for clinical study under Protocol Nos. PAR-03 and PAR-04.
July 12, 1985	Submitted amendment to Notice of Claimed Investigation to provide for extension study under Protocol No. PAR-02.
July 17, 1985	Submitted revised amendment (Informed Consent form) to be utilized under Protocol No. PAR-02, by James L. Claghorn, M.D.
July 17, 1985	Submitted revised amendment for clinical studies to be conducted under Protocols No. PAR-02, PAR-03, PAR-04, PAR-05 and PAR-09. Revision provides for inclusion of one assistant to the principal investigator.
July 23, 1985	Submitted amendment to include nine additional physicians as participating clinical investigators to be conducted under Protocol No. PAR-02-01.
July 29, 1985	Submitted revised amendment to provide for a change in the dosing statement of Protocol No. PAR-05.

July 31, 1985	Submitted amendment which provides for the replacement of Dr. Stephen Swenson with Ms. Victoria Pearson as assistant to Dr. Halikas in conducting a clinical study under Protocol PAR-09.
August 20, 1985	Submitted amendment to remove the restriction of women of child-bearing potential from the clinical protocols.
September 3, 1985	Received correspondence from FDA pertaining to Protocol PAR-03 & Protocol PAR-04 regarding FDA previous submissions.
September 4, 1985	Submitted revision to provide for inclusion of new co-investigator, Jack Conway, M.D. under Protocol No. PAR-09.
October 4, 1985	Submitted revised amendment to provide for the inclusion of two additional investigators (Dr. Ezell and Ievoli).
November 1, 1985	Submitted amendment to add one additional physician, Michael Helzner.
November 13, 1985	MEP telephone conversation with Tony DeCicco re: removal of restriction on women of child-bearing potential from protocols. Mr. DeCicco advised letter would issue within the next few weeks to confirm.
November 20, 1985	Agency letter - Advising that women of child-bearing potential may be entered into study. From Paul Leber, M.D., Director, FDA.
November 22, 1985	Response to Agency's letter of 8-27-85, by Dr. Ron Jackson, Medical Dept.
December 19, 1985	Amendment submitted to include co-investigator, Richard Alexander, M.D.
December 19, 1985	Amendment submitted to include four co-investigators, Joseph Hassman, DO; Jerry London, DO; Barry Montague, DO and Charles Weise, M.D.
February 13, 1986	Submitted 4 DER's (patient nos. 059, 030, 009 and 062) under Prot. nos. 03-03, Dr. Mendels; 05-01A, Dr. Bremner; 04-01 Dr. Merideth; and 03-01, Dr. Merideth.

February 24, 1986	Submitted Annual Progress Report covering Dec. 1984-Dec. 1985.
February 24, 1986	Submitted revised amendment to provide for clinical studies to be conducted under Prot. PAR-03 and PAR-04 by Dr. Mendels.
March 17, 1986	Submitted revised amendment to include James M. Ferguson, M.D., to assist Dr. Feighner in Protocol PAR-03, PAR-04 and PAR-09.
March 26, 1986	Submitted revision to Prot. PAR-05 to limit the use of chloral hydrate as a sleep aid on a rare episodic basis. Principal investigators: Dr. Bremner and Dr. Feighner.
March 26, 1986	Submitted amendment to revised protocol PAR-04 for studies to be conducted by Drs. Cohn, Fabre, Fieve, Feighner, Mendels and Shrivastava. Revision limited the use of chloral hydrate as a sleep aid on a rare episodic basis.
March 31, 1986	Submitted 5 DER's Pt. #402, Dr. Alexander; #034, Dr. Crowder; #148, Dr. Filippi; #405, Dr. Cunningham; and #017, Dr. Bremner.
April 2, 1986	Submitted two Drug Experience Reports, Complaint Nos. PAR-09-01J-596 and PAR-09-01J-614. A. Kahn, M.D. was the investigator for both.
April 3, 1986	Submitted amendment providing for the two animal pharmacology reports and a mouse carcinogenicity study to be included in original IND submission.
April 11, 1986	Submitted revised amendment to provide for the inclusion of David J. Marion, Ed.D., under studies to be conducted by Joseph Mendels, M.D. Prot. Nos. PAR-03 and PAR-04.
April 16, 1986	Submitted amendment to provide for additional Phase 2 study to be conducted by Ari Kiev, M.D. under Prot. PAR-02.
April 16, 1986	Submitted Drug Experience Report for Mfr. Control No. PAR-04-03-040 in studies conducted by Dr. Mendels.
June 3, 1986	Submitted 3 initial Drug Experience Reports for patients enrolled in clinical studies under Drs. Cohn, Settle, & Bremner.

June 17, 1986	Submitted Drug Experience Report for patient #056 under Dr. Cohn.
June 27, 1986	Submitted revised amendment to provide for patients participating in on-going study to continue on open-label for an additional one-year period.
July 11, 1986	Submitted amendment revision to Protocols PAR-04 and PAR-05 in triplicate.
July 29, 1986	Submitted DER on patient #620, Dr. David Dunner.
August 12, 1986	Submitted Drug Experience Reports for 3 patients: (#'s 83, 99, 100).
August 22, 1986	Submitted amendment to provide for extensions of 2 clinical studies and increase in number of patients in a third study. (Protocol PAR-04 and PAR-05). Also to amend IND 23,280 to provide for new study to be conducted by Vernon E. Grove, M.D.
September 4, 1986	Submitted Follow-up Drug Experience Report, Patient #620 under Protocol No. PAR-04-02, Investigator: David Dunner, M.D.
September 5, 1986	File memo from MEP. Phone call from Tony DeCicco, CSO-FDA requesting additional copy of 6-27-86 IND amendment. Copy mailed this date.
September 5, 1986	Resubmission of 6-27-86 IND Amendment per request to Mr. Anthony W. DeCicco, FDA.
September 10, 1986	Submitted Drug Experience Reports for 2 patients: (#079, #087).
September 12, 1986	Submitted amendment Notice of Claimed Investigational Exemption for a new study to be conducted by David L. Dunner, M.D. Also two additional studies conducted under Protocol No. PAR-05. Investigators will be Walter A. Brown, M.D. and Joseph Mendels, M.D.
September 19, 1986	Submitted Notice of Claimed Investigational Exemption to provide for a one-year extension of a study conducted by John P. Feighner, M.D. under Protocol PAR-04.

September 24, 1986	Submitted amendment of Notice of Claimed Investigational Exemption for a one-year open-label extension of a study conducted by Ronald S. Fieve, M.D. under Protocol No. PAR-04.
October 1, 1986	Submitted Amendment to Notice of Claimed Investigational Exemption to provide for an additional study to be conducted by J. B. Cohn, M.D. under Protocol No. PAR-06.
October 10, 1986	Submitted amendment to provide for new investigation under Dr. Joseph Mendels' Protocols PAR-03, 04, and 05. Dr. Janice Horowitz will assist Dr. Mendels under these protocols.
October 10, 1986	Submitted amendment to provide for three additional clinical studies under protocols previously filed with Agency. (PAR-05, 06, 07). Studies will be done by Ward T. Smith, M.D. and Eric C. Dessain, M.D.
October 24, 1986	Received comments from Agency regarding submissions of September 12 and October 1, providing for Protocols Nos. PAR-05, 06, and 07.
October 29, 1986	Submitted amendment to provide for study under Protocol PAR-05 by Ari Kiev, M.D.
November 5, 1986	Submitted Notice of Claimed Investigational Exemption to Protocol No. PAR-05 for study by Alan D. Feiger, M.D.
November 12, 1986	Submitted Notice of Claimed Investigational Exemption to Protocol No. PAR-05 for study by Ronald R. Fieve, M.D.
November 25, 1986	Submitted amendment to provide for revision in Protocol No. PAR-06 showing line in the table on page 21, Section III.C.2 as being deleted.
December 11, 1986	Submitted amendment to provide for additional study under Protocol No. PAR-05 by Lynn A. Cunningham, M.D.
December 15, 1986	Submitted DER for patient #097 (SVD), Protocol No. PAR-04-05, Principal Investigator: Ronald R. Fieve, M.D.

December 16, 1986	Submitted Amendment to provide for inclusion of two new investigators, John A. Boston, Jr., M.D., and Scott Elkin, D.O. to provide for a study to be conducted under Protocol PAR-05.
January 5, 1987	Submitted Amendment to provide additional study under Protocol No. PAR-05 by Murray H. Rosenthal, D.O., APC. Also amendment to provide for an additional co-investigator, Dr. Barry G. Chaiken, to assist Dr. Ronald R. Fieve under Protocol PAR-03, 04, and 05.
January 15, 1987	Submitted Notice of Claimed Investigational Exemption to provide for a revision to Protocol PAR-05-02 initially submitted on 7-29-85.
January 27, 1987	Submitted amendment to provide for a revision in the wording of Protocol PAR-06 initially filed on 10/1/87.
February 4, 1987	Submitted DER's for patients #002 (BMJ), Protocol No. PAR-05-02F, Principal Investigator: Alan D. Feiger, M.D. and #070 (BBB), Protocol No. PAR-03-05, Principal Investigator: Ronald R. Fieve, M.D.
February 11, 1987	Submitted Amendment to designate Vincent P. Houser, Ph.D as monitor for all clinical studies on this investigational new drug product.
February 13, 1987	Submitted Amendment to provide for a new Phase 2 study by Marvin C. Meyer, Ph.D under Protocol PAR-08 and additional Phase 3 study by Ferris N. Pitts, M.D., under Protocol PAR-07. In addition to these, amendment was made to provide for 2 new co-investigators, Elia S. Toueg, M.D. and John R. Stabile, M.D. to assist Dr. Ari Kiev under Protocol PAR-02.
February 18, 1987	Submitted Amendment to record new addresses for two investigators: Lynn A. Cunningham, M.D. and Vernon E. Grove, M.D.
February 20, 1987	Submitted Annual Progress Report covering period from December 1985 to December 1986.
February 26, 1987	File memo from MEP regarding telecon between MEP and Tony DeCicco - CSO to obtain indentity of the medical officer assigned to our Paroxetine IND 23,280.

March 16, 1987	Submitted DER providing details on patient #033 (CSO).
April 8, 1987	Submitted amendment to provide for a revision in Protocol PAR-07 being conducted by Dr.'s Smith, Dunner and Pitts.
April 9, 1987	Received copy of letter to Richard Kapit, M.D., FDA from Dr. Ron Jackson regarding a follow-up to their telecon of 2/27/87 and 4/4/87. A report was sent regarding the high incidence of gastrointestinal and CNS adverse experienced in the study being concucted at UT Center for Health Sciences, Memphis, TN.
April 9, 1987	Submitted amendment to provide for increase in patient enrollment from 20 to 30 under PAR-05 by Ward T. Smith, M.D.
April 24, 1987	Submitted DER on patients #017 (BMS) and #001 (ECH).
April 24, 1987	Submitted amendment to provide for increase of patient enrollment to 50 in study underway by Walter A. Brown, M.D. under PAR-05.
May 1, 1987	Submitted amendment for investigational new drug to provide a new study to be conducted by Jerry M. Herron, M.D. This study will be conducted under Protocol PAR-12-01, entitled "A Placebo-Controlled, Single Dose, Five-Period Crossover Evaluation of the Pharmacokinetic Properties of Paroxetine When Administered by Oral Route."
May 5, 1987	Submitted DER on patient #089 (BUR), study conducted by Ari Kiev, M.D., Protocol No. PAR-02-04.
May 6, 1987	Submitted amendment for a revision in Protocol PAR-05, entitled "An Open Label Longterm Evaluation of Paroxetine in Depressed Outpatients." This protocol was initially submitted to the Agency on 4-25-85.
June 2, 1987	Submitted amendment to Agency to provide an updated copy of the Clinical Brochure No. 3-024 dated May 1987.

June 5, 1987	Submitted amendment to Agency to provide for the inclusion of an additional co-investigator, Alvin W. Strauss, M.D. to assist Dr. Jerry M. Herron in his ongoing study under Protocol PAR-12.
June 9, 1987	Submitted amendment to Agency to provide for the replacement of the principal investigator, Vernon E. Grove, M.D., with Scott Elkin, D.O., under Protocol No. PAR-05.
June 9, 1987	Submitted amendment to Agency to include a new co-investigator, Francis X. Haines, M.D., in our ongoing study by Dr. Walter A. Brown under Protocol No. PAR-05.
June 22, 1987	Submitted amendment to provide for an additional two-year continuation of patients enrolled in the ongoing study under Protocol No. PAR-05.
June 22, 1987	Submitted to Agency DER on two patients enrolled in clinical study, Mfg. Control No. PAR-05-02J-15 Patient #015 (KFT) and Mfg. Control No. PAR-05-02J-020 Patient #020 (KMC).
June 24, 1987	Submitted corrected copy of cover letter for two amendments filed on IND 23,280 dated June 9, 1987.
June 24, 1987	Submitted amendment to provide a revised Form FDA 1573 under Protocol PAR-05-02C.
July 10, 1987	Submitted DER on patients #113 (JEJ) and #033 (CSO).
July 31, 1987	Submitted DER providing details on five patients #093 (CH), #015 (MHS), #013 (MLO), #019 (RS) and #010 (LSG).
August 4, 1987	Submitted amendment to include two new studies, Protocol No. PAR-10-01 - "A Multi-Dose Steady-State Design Pharmacokinetic, Evaluation of the Interaction Between Paroxetine and Diazepam" and Protocol No. PAR-11-01B "A Multi-Center, Doxepin Controlled, Double-Blind Study of Paroxetine in Geriatric Outpatients with Major Depressive Disorders."
August 11, 1987	Submitted DER on patient #015 (BJL).

August 26, 1987	Submitted amendment on updated copy of Form FDA 1573 signed by Dr. Walter A Brown under Protocol No. PAR-05.
September 2, 1987	Submitted amendment to provide for a replacement protocol and 9 additional studies to be conducted under Protocol-11-01.
October 9, 1987	Submitted protocol amendment for a change in Protocol PAR-10-01 filed on August 4, 1987 and conducted by James C. Kisicki, M.D.
October 12, 1987	Submitted protocol amendment to provide for a new study under Protocol PAR-13-01 conducted by James C. Kisicki, M.D.
October 13, 1987	Submitted protocol amendment for a change in Protocol PAR-05-02 to allow patients to continue on open-label Paroxetine therapy for an additional 3 years, i.e., up to 4 years of therapy. Drs. Walter A. Brown and Scott Elkin will utilize this new change in their study plan.
October 21, 1987	Submitted protocol amendment for an extension in a study by John P. Feighner, M.D. under Protocol PAR-05-01B. Also, two new investigators have been added to Dr. Feighner's study: Drs. Wm. F. Boyer and Thomas A. Flanagan.
October 22, 1987	Submitted protocol amendment to provide for extensions in 2 studies under Protocol PAR-05 by Drs. Joseph Mendels and Ari Kiev.
November 6, 1987	Dr. Powell submitted Possible IND Safety Report to FDA on a 54-year old male patient experiencing blurred vision. Full report will follow.
November 9, 1987	Submitted Change in Protocol, Serial No. 006, to provide for an extension in a study conducted by Ward T. Smith, M.D. under Protocol No. PAR-05-02D.
November 9, 1987	Submitted Follow-up DER on two patients enrolled in a clinical study, conducted by Dr. Walter A. Brown, identified as PAR-05-02A-013 and PAR-05-02A-015. (For In-house record purposes these have been assigned Ref. Nos. 3654 and 3656.)

November 23, 1987	Submitted Change in Protocol, Serial No. 007, to provide for extension in a study conducted by Alan D. Feiger, M.D. under Protocol No. PAR-05-02F.
November 25, 1987	Dr. Powell submitted follow-up letter to FDA in reference to our letter of Nov. 6, 1987, in which we notified the Div. of a possible IND Safety Report. A full evaluation was provided to the FDA.
December 4, 1987	Submitted Change In Protocol, Serial No. 008, to provide for an addendum to the informed consent forms utilized in two ongoing studies conducted under PAR-04 and PAR-05.
December 16, 1987	Submitted Change In Protocol, Serial No. 009, to provide for extensions in two Phase III studies and one Phase II study under Protocol PAR-04 and PAR-05. Ronald R. Fieve, M.D. and Lynn A. Cunningham, M.D. are the investigators.
January 15, 1988	Submitted Correction, to Serial No. 009, dated Dec. 16, 1987.
January 21, 1988	Submitted Change in Protocol, Serial No. 010, to provide for a two-year extension for PAR-04-01.
January 22, 1988	Submitted Change in Protocol, Serial No. 011, to provide additional exclusion criteria in evaluating whether patients are acceptable candidates for entry into this investigation.
January 25, 1988	Submitted New Protocol, Serial No. 012, to provide for a new clinical study protocol: PAR-14-01, conducted by James C. Kisicki, M.D.
January 27, 1988	Submitted Change in Protocol, Serial No. 013, to provide expansion of criteria for PAR-06-01A - Jay B. Cohn, M.D., Ph.D., and PAR-06-01B - Eric C. Dessain, M.D.
February 19, 1988	Submitted Information Amendment: Clinical Supplies Procedure, Serial No. 014, to provide for change(s) protocol PAR-05-02H conducted by Murray Rosenthal, D.O. Also provided the addition of James J. Hudziak, M.D., as an additional investigator.

February 29, 1988	Submitted Annual Progress Report for the year 1987.
March 3, 1988	Submitted Protocol Amendment: New Protocol, Serial No. 016, to provide for a new clinical study under PAR-15-01 by James C. Kisicki, M.D.
March 14, 1988	Submitted Information Amendment: Chemistry, Manufacturing, and Control, Serial No. 017, to provide information regarding an alternative route of synthesis for paroxetine hydrochloride.
March 14, 1988	Submitted Protocol Amendment: Protocol Revision, Serial No. 018, to provide for an increase in patient enrollment from 50 to 90 in the clinical study PAR-05-02A applicable only for Walter A. Brown, M.D.
March 31, 1988	Submitted Information Amendment: Pharmacology-Toxicology-Clinical, Serial No. 019, to provide additional data regarding this product
April 13, 1988	Submitted Protocol Amendment: Change in Protocol, Serial No. 020, to provide for a new principal investigator, Thomas M. Walshe, III, M.D., for Protocol PAR-06-01B.
April 26, 1988	Submitted Protocol Amendment: Protocol Revision, Serial No. 021, to provide for an increase in patient enrollment from 30 to 60 patients in study underway for PAR-05-02D and will apply only for investigator, Ward T. Smith, M.D.
May 11, 1988	Submitted Amendment: Protocol Revision, Serial No. 022, to provide for an increase in patient enrollment from 20 to 40 patients in study underway for PAR-05-02F, and will apply only for investigator, Alan D. Feiger, M.D..
June 10, 1988	Submitted Change in Protocol Nos. PAR-05-02F, 11-01A and 11-01E, Serial No. 023.
July 1, 1988	Submitted Information Amendment, Clinical Brochure, Serial No. 024.
July 26, 1988	Submitted Change in Protocol, PAR-05-02C and PAR-06-01B, Serial No. 025.

Paroxetine Tablets IND 23,280

August 2, 1988	Submitted Change in Protocol, PAR 11-01A, Serial No. 026.
Aug. 26, 1988	Memo to Dr. Gundersen from Dr. Mannion regarding telephone conversation between Mr. Tony DeCicco, COS FDA, and Dr. Mannion.
Sept. 2, 1988	Letter to Paul D. Leber, M.D., FDA, from Dr. Powell to request a pre-NDA meeting, Serial no. 027.
Sept. 19, 1988	Protocol/Information Amendment. Correction to packaging and labeling PAR 04 also a completed clinical/statistical report on PAR 01-01. Serial No. 028.
Sept. 29, 1988	New protocol PAR 16-01: "A Multiple-Dose, Steady-State, Cross-Over, Replicate-Sample Evaluation of the Bioequivalence of a Caplet and Capsule Formulation of Paroxetine." Investigator...Jerry M. Herron, M.D, Serial No. 029.
Oct. 7, 1988	Sent 4 copies Paroxetine IND Amendment (6.2, 6.3, 6.4, 6.5) to Dr. Andrea M. Powell request from Division staff. Originally submitted March 31, 1988.
Oct. 17, 1988	Call to FDA to Dr. Andrea Powell to verify receipt of 4 copies of Paroxetine sent 10/7/88.
Oct. 20,1988	Amendment to PAR 11-01D. Serial no. 030. Updated 1572 and CV for Dr. Robert H. Levy, new co-investigator.
Nov. 2, 1988	Letter to Paul L. Leber, M.D. (FDA) to confirm pre-NDA meeting scheduled for November 17, 1988.
Nov. 14, 1988	FDA telephone conversation with Mr. Tony DeCicco regarding FDA's preparatory pre-NDA meeting on Paroxetine.
Nov. 15, 1988	Information amendment for PAR 16-01 to provide for the formulation and manufacture of the 30 mg Paroxetine tablet. Serial no. 031.
Dec. 1, 1988	Letter to Dr. P. Leber (FDA) regarding the format and content of an individual study report. Prototype PAR 03.001....Serial no. 032.

Paroxetine Tablets IND 23,280

Dec. 15, 1988	Letter from Paul Leber, M.D. re: Nov. 17, 1988 Pre-NDA Meeting minutes, Nov. 29, 1988 teleconference and Dec. 1, 1988 amendment.
Jan. 6, 1989	Information amendment: FDA letter to Dr. P. Leber with tablet stability tables to be used in NDA. **Serial no. 033.**
Jan. 31, 1989	Telephone conversation with Mr. Robert Young, FDA. Requested to provide information to FDA on investigator Dr. Cal Cohn. (protocol 11)
Feb. 3, 1989	FDA converation record with Mr. Robert Young. Info given about patient enrollment in protocol 11. Mr. Young requested the same type of info on Dr. R. Fieve, investigator on PAR 03- PAR 04.
Feb. 9, 1989	Mr. Robert Young requested by telephone a copy of the 1572 for Dr. Fieve (PAR 03-PAR 04).
Feb. 10, 1989	Letter forwarded to Mr. Robert Young (FDA) regarding Ronald R. Fieve, M.D., investigator for PAR 03-PAR 04.
Feb. 16, 1989	Telephone conversation (Mr. R. Young, FDA) in which Mr. Young requested CRFs from PAR 03 and PAR 04.
Mar. 2, 1989	Telephone conversation with Stan Blum, FDA Chemistry Review Officer for Paroxetine Tablets.
Mar. 3, 1989	Telephone conversation with Carol Currier (Clinical Investigations Branch) regarding status of the CRFs requested by Mr. R. Young.
Mar. 9, 1989	Letter to Mr. R. Young (FDA) accompanying the CRFs for Dr. Ronald R. Fieve (PAR 03- PAR 04)
Mar. 17, 1989	Annual Progress Report **Serial no. 034**
Mar. 30, 1989	Change in protocol. **Serial no. 035.** Revised FDA Form 1572's and CVs for new co-investigators. PAR 06-01B PAR 11-01B

Apr. 28, 1989	Revised 1572 for PAR 03-02. John E. Crowder, M.D. added as co-investigator. **Serial no. 036**
Sept. 1, 1989	Sent Dr. Tina Blumhardt's CV as new monitor for Paroxetine. **Serial no. 0037**
Oct. 23, 1989	Call to CSO Tony Dicicco to alert him that the NDA for Paroxetine would be submitted in November and to verify where it should be sent.
Nov. 21, 1989	NDA submitted to FDA (954 volumes).
Dec. 1, 1989	Call to FDA to discuss time schedule for safety update. We were told to await further instructions from FDA before submitting.
Jan. 2, 1990	Received call from Martin Brecker, M.D., Medical Officer assigned to Paroxetine. Characterization of NDA by Dr. Brecker. "NDA looks terrific in terms of orgainization." "No glaring omissions." "Looks very clean." List of nine questions submitted to Dr. Mannion.
Jan. 5. 1990	Verbal response to FDA questions by Dr. Brecker. Answers sent directly to Dr. Brecker, no formal submission made.
Jan. 8, 1990	Letter response (not formal submission) to request for information from Dr. Brecker.
Jan. 12, 1990	After review of our response, Dr. Brecker had more questions which I responded to via telephone converesation.
Jan. 18, 1990	Letter to Dr. Martin Brecher containing material requested by FDA. Not a formal submission.
Jan. 19, 1990	Arrangements made via telephone for Dr. Donnelly to meet with Dr. Brecher on January 22,1990
Jan. 26, 1990	Returned call to Dr. Brecher to answer questions concerning ECG studies.
Jan. 29, 1990	New questions from Dr. Brecher regarding NDA. Dr. Brecher noted that the NDA was officially filed and he gave Dr. Donnelly a list of reviewers for different sections of the NDA.
Jan. 29, 1990	Call to Jay Lavine, Statistical Reviewer, for Paroxetine to arrange a brief meeting with him on February 2,1990.

U.S. Regulatory Affairs

SmithKline Beecham Pharmaceuticals

MEMORANDUM

PAXIL (Paroxetine Hydrochloride) Tablets
NDA 20-031
SUBMISSION HISTORY
AS OF OCTOBER 15, 1992

November 20, 1989	NDA 20-031 Submission
December 1, 1989	Correspondence with Dr. Paul Leber regarding the timing of the initial safety update.
January 8, 1990	Correspondence with Dr. Martin Brecher regarding trial design of US studies and protocol violators. (Copy submitted to Dr. Leber 11/28/90)
January 18, 1990	Correspondence with Dr. Brecher concerning design of non-US clinical studies and investigator terms for certain COSTART designations. (Copy submitted to Dr. Leber 11/28/90)
January 30, 1990	Correspondence with Dr. Brecher providing clarification concerning patient ID numbers and demographic information. (Copy submitted to Dr. Leber 11/28/90)
February 27, 1990	Correspondence with Dr. Brecher re gender specific adverse events, myocardial infraction, weight changes, hypertension, chest x-rays, serotonin syndrome, zimelidine syndrome. (Copy submitted to Dr. Leber 11/28/90)
March 6, 1990	Submission of a revised Table of Contents for the Statistical Section of the NDA.
March 9, 1990	Correspondence with Dr. Brecher concerning lab values and changes, ECG changes, serious adverse events and gender specific adverse experiences. (Copy submitted to Dr. Leber 11/28/90)
March 19, 1990	Correspondence with Dr. Robert Young, Office of Scientific Investigations concerning pivotal trials.
March 22, 1990	Correspondence with Dr. Gary Evoniuk providing pages from preclinical study BRL 918-G/821002.
April 12, 1990	Correspondence with Dr. Young concerning protocols for PAR-01, 02 and 03.
April 24, 1990	Correspondence with Dr. Young concerning the summaries of the safety, efficacy and statistical analysis of PAR-09.
May 2, 1990	Correspondence with Dr. Young concerning PAR 02-01, 03-01 and 03-02.

May 17, 1990	Correspondence with Dr. Stan Blum concerning the synthesis of labeled paroxetine. (Copy submitted to Dr. Leber 11/28/90)
May 22, 1990	Correspondence with Dr. Leber re preclinical carcinogenicity data on disk.
June 20, 1990	Correspondence with Dr. Leber concerning meeting on June 26, 1990 to present the Computer Assisted NDA for paroxetine to the Division.
June 22, 1990	Correspondence with Dr. Brecher concerning US safety database, ophthalmic changes, vital signs, CPK changes. (Copy submitted to Dr. Leber 11/28/90)
August 8, 1990	Correspondence with Dr. Leber concerning preclinical carcinogenicity studies.
August 9, 1990	Correspondence (14 volumes) with Dr. Leber re questions received from Dr. Brecher concerning chest X-rays, physical exams, weight changes, further details on specific patients, case report forms, narratives for serious adverse experiences.
August 30, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning serious adverse experiences, patient ID numbers, single vs double flags, lab abnormalities, hematology.
August 31, 1990	Request for guidance from FDA re the requirements for certain chemistry, manufacturing and controls issues: alternate manufacturing site at Cidra, PR, production validation protocol and the impact of minor changes in the drug product manufacturing process.
September 12, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning safety issues.
September 21, 1990	Correspondence with Dr. Leber re questions received from Dr. G. Evoniuk concerning a preclinical carcinogenicity study.
September 24, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning hematology, physical exams, serious adverse experiences.
October 24, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning case reports and weight gain.
November 16, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning various efficacy trials.
November 27, 1990	Correspondence with Dr. Leber re questions received from Dr. Kusuma Mallikaarjun concerning analysis of paroxetine, and product labeling.
November 28, 1990	Submission to Dr. Leber of copies of previous submissions made directly to Drs. Brecher and Blum on January 8, 17, and 30, February 2, and 27, March 9, May 17 and June 22, 1990.

November 30, 1990	Submission of initial safety update (26 volumes) to the NDA.
December 19, 1990	Submission to Dr. Leber of preliminary data and publications concerning human cytochrome P450IID6 in general and its inhibition by paroxetine as well as other SSRIs.
December 20, 1990	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning efficacy trials.
January 7, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning pharmacokinetic reports of efficacy trials, morning vs evening dosing, adverse events in the elderly.
January 8, 1991	Submission to Dr. Leber of additional stability data on paroxetine tablets produced in Bristol, TN.
January 10, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning seizures, lab values, efficacy results.
February 19, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning statistical analysis of PAR-09.
February 28, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning safety and efficacy.
March 27, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning patients with breast cancer.
April 1, 1991	Submission of an expanded version of the table of contents for the Statistical Section of the NDA for use by Mr. Ken Petronis (previously submitted for use by Jay Levine, March 6, 1990).
April 5, 1991	Submission to Dr. Leber of SAS code documentation used to produce the efficacy results in the paroxetine CANDA which had been requested by Mr. Petronis.
April 12, 1991	Correspondence with Dr. Leber re questions received from Dr. K. Mallikaarjun concerning batch, lot and formulation numbers used in biopharmaceutics and bioequivalence trials; shape of tablets used and ambiguous protocol numbers.
May 3, 1991	Correspondence with Dr. Leber re questions received from Dr. Brecher concerning adverse experiences noted in the IND Annual Report.
May 10, 1991	Correspondence with Dr. Leber re request from Dr. Brecher for a position paper on suicidal ideation and behavior.
May 30, 1991	Correspondence with Dr. Leber concerning request received from Dr. Brecher concerning an analysis of the incidence of cancer occurrences in the paroxetine clinical trials.
June 7, 1991	Submission of an amendment providing for the manufacturing, processing and packaging of paroxetine tablets at Cidra, PR facility.

June 11, 1991	Correspondence with Mr. R. Young concerning the principal investigator and all co-investigators associated with studies PAR 02-01 (Rickels) and PAR 02-04 (Kiev).
June 17, 1991	Correspondence with Dr. Leber re request from Dr. Brecher concerning re-analysis of the incidence of cancer in the paroxetine clinical trials program.
June 27, 1991	Correspondence with Dr. Leber re request from Mr. J. Levine for a table summarizing an analysis of the HAMD depressed mood item using the visit wise dataset of the intent to treat population in the studies of the PAR-01, PAR-02 and PAR-03 series.
July 2, 1991	Correspondence with Dr. Leber re request from Mr. Levine for data listings from the PAR 02-003 (Smith) report.
July 11, 1991	Correspondence with Dr. Leber re content and format of second (final) safety update on paroxetine.
July 11, 1991	Correspondence with Dr. Leber withdrawing request for approval of facilities at Bristol, TN as site of manufacturing, processing and packaging of paroxetine hydrochloride tablets.
July 16, 1991	Correspondence with Dr. Leber re request from Mr. Levine for a re-analysis of PAR 02-001 (Rickels) as a multi-center or multi-sub-investigator study with terms for for treatment, subinvestigator and interaction.
July 22, 1991	Submission of an amendment for the addition of the 40 mg tablet to the four strengths (10, 20 30 and 50 mg) in the NDA.
July 30, 1991	Correspondence with Dr. Leber re request from Dr. Blum for minutes and copies of overheads from the June 18, 1991 meeting between SB, Stanley Blum and Paul David. An expanded table of contents for the CMC section was also included.
September 26, 1991	Correspondence with Dr. Leber re request from Dr. Mallikaarjun concerning various pharmacokinetic parameters in report of the bioequivalence trial PAR-16.
October 4, 1991	Correspondence with Dr. Leber requesting approval for a new proprietary name (PAXIL) for paroxetine hydrochloride tablets.
October 15, 1991	Correspondence with Dr. Leber re request from Dr. Mallikaarjun for pharmacokinetic data from PAR-16 on a PC diskette.
October 25, 1991	Correspondence with Dr. Leber re request from Dr. Mallikaarjun for pharmacokinetic data from PAR-12 on a PC diskette.
November 1, 1991	Correspondence with Dr. Leber re request from Dr. Blum for additional stability data from Cidra, list of clinical studies and route of synthesis for chemical substance used in clinical supplies, and impurity profiles of batches of paroxetine synthesized by various routes.

December 18, 1991	Correspondence with Dr. Leber re request from Dr. E. Nevius for computer data disks of selected paroxetine clinical trial efficacy datasets.
December 20, 1991	Correspondence with Dr. Leber re request from Dr. Nevius for revised computer data disks of selected paroxetine clinical trial datasets.
December 20, 1991	Submitted amendment for addition of alternate site of manufacture (Penn Chemicals, Ireland) for the first three stages of the seven stage route "C" synthesis of bulk drug substance.
January 20, 1992	Correspondence with Dr. Leber re request from Dr. Blum concerning identity test and specification for optical purity for all strengths of finished tablets, and revised specifications for finished product.
January 31, 1992	Submission of revised labeling for PAXIL (paroxetine hydrochloride) Tablets.
February 5, 1992	Correspondence with Dr. Leber re request from Mr. P. David concerning copies of preclinical studies addressing potential carcinogenicity in rats and mice.
February 6, 1992	Correspondence with Dr. Leber re request from Mr. David concerning portion of the Summary of Toxicology addressing carcinogenicity studies in rats and mice.
February 12, 1992	Correspondence with Dr. Leber re issues arising from the meeting (12/26/91) with Dr. S. Blum and SB concerning the Penn Chemicals submission.
February 13, 1992	Submission of second (final) safety update including case report forms as appropriate.
February 14, 1992	Correspondence with Dr. Leber re request from Dr. Mallikaarjun concerning the clinical capsule in PAR 16, dissolution profiles of tablets in three media, statistical information concerning studies HP/85/3 and HP/85/2, and distribution of paroxetine between plasma and cellular fractions of blood.
February 21, 1992	Correspondence with Dr. Leber re request from Mr. David for copies of statistical summaries to preclinical carcinogenicity studies in rats and mice.
March 9, 1992	Submission of revised draft labeling including the annotated version.
March 9, 1992	Submission of a draft Summary Basis of Approval.
March 11, 1992	Submission of 10 copies of the draft Summary Basis of Approval and 10 copies of the journal supplement: "A Clinical Profile of Paroxetine: A Novel Selective Serotonin ReUptake Inhibitor" from the J. Clinical Psychiatry 53: February 1992.

March 16, 1992	Correspondence with Dr. Leber re request from Dr. Blum concerning flow chart identifying batches of each stage of material used to produce batch 91-0023 of paroxetine drug substance with quantities input and yield at each stage.
March 24, 1992	Submission of export application to permit export of paroxetine tablets to Canada.
April 8, 1992	Submission of information amendment containing two reports describing preclinical studies and 14 reports describing results of clinical studies. Ten of these clinical reports are addenda to reports already filed in the NDA.
May 6, 1992	Submission of several revisions to the amendment of December 20, 1992 concerning the Penn Chemicals facility.
May 12, 1992	Correspondence with Dr. Leber re request from Dr. Blum concerning IR method for the identification of paroxetine in finished tablets, TLC method for determining dyes in Opadry, and updated stability data for tablet lots produced at Cidra, P.R.
June 19, 1992	Correspondence with Dr. Leber re request from Dr. Mallikaarjun concerning dissolution data in three media, comparison of dissolution data from 50 mg tablet from Bristol and Cidra.
July 2, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 13, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 15, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 17, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 21, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 23, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 24, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 29, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
July 30, 1992	Correspondence with Dr. Leber re request from Dr. Blum concerning stability protocol for chemical substance, possible use of recovered solvents, sample chromatograms, in-process controls, and other CMC issues.
August 3, 1992	Submission of draft sample carton and immediate container labels.
August 6, 1992	Correspondence with Dr. Leber re requests from Dr. Blum concerning sample chromatograms for the various chromatographic methods; information linking route of synthesis, lot number of drug substance, lot number of drug product and study number (clinical or pre-clinical).

August 11, 1992	Correspondence with Dr. Leber re request from Dr. Mallikaarjun for dissolution data in three media for tablets produced in Bristol, TN.
August 19, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
August 20, 1992	Submission of sponsor's agenda for the Advisory Committee meeting.
August 26, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
August 28, 1992	Submission of an amendment providing revised drug product manufacturing conditions.
September 2, 1992	Correspondence with Dr. Leber re request from Ms. Joy Mele for dosing information and mean weight at baseline for PAR-01, -02 and -03.
September 3, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
September 8, 1992	Correspondence with Dr. Leber re request from Dr. Nevius for copies of materials originally submitted on July 16, 1991 concerning re-analysis of Study PAR 02-001.
September 14, 1992	Correspondence with Dr. Laughren concerning SBA revisions.
September 16, 1992	Correspondence with Dr. Laughren concerning SBA revisions and hardcopy of revised SBA text and all tables.
September 17, 1992	Correspondence with Dr. Leber re request from Ms. Mele for pooled efficacy data for studies PAR-01, -02 and -03.
September 18, 1992	Correspondence with Dr. Leber re request from Ms. Mele for efficacy and demographic data from study PAR-083.
September 29, 1992	Correspondence with Dr. Leber re request from Ms. Mele for additional analyses concerning possible relationship between plasma levels of paroxetine and safety and efficacy.
October 13, 1992	Correspondence with Dr. Laughren concerning SBA revisions and Advisory Committee presentation.

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1993
PAT. & TRADEMARK OFF.

James 5507 9200 10-28-93 9200

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

06/922530

In re: U.S. Patent No. 4,721,723
Issued: January 26, 1988
To: Roger D. Barnes et al
For: Anti-depressant Crystalline Paroxetine Hydrochloride

93 APR 30 PM 7:17

February 22, 1993

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

RECEIVED
APR 15 1993
APPLICATION DIVISION

Re: Deposit Account No. 19-2570
SmithKline Beecham Corporation
(a sister corporation of Beecham Group p.l.c.)
U.S. Patent No. 4,721,723

Sir:

Transmitted herewith is an original application for extension of patent term under 35 U.S.C. 156 with regard to U.S. Patent No.4,721,723 and one photocopy thereof.

Please charge my Deposit Account No. 19-2570 in the amount of $1,000.00. The Commissioner is hereby authorized to charge any additional fees, which may be required, or credit any overpayment to Account No. 19-2570. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

BEECHAM GROUP p.l.c.

By: Edward T. Lentz

Edward T. Lentz
Attorney for Applicant
Registration No. 30,191

SmithKline Beecham Corporation
Corp. Patents-U.S. - UW2220
P.O. Box 1539
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9 FEB 22 1993 PAT. & TRADEMARK OFF.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent No. 4,721,723
Issued: January 26, 1988
To: Roger D. Barnes et al
For: Anti-depressant Crystalline Paroxetine Hydrochloride

February 22, 1993

Commissioner of Patents and Trademarks
Box Patent Extension
Washington, D.C. 20231

93 APR 30 PM 7:18

CERTIFICATION

The undersigned hereby certifies that the attached phocopy is an exact duplicate of the application for extension of the term of U.S. Patent 4,721,723 under 35 U.S.C. 156, including its attachments and supporting papers, mailed to the U.S. Patent and Trademark Office herewith on this date.

Date: February 22, 1993

Edward T. Lentz

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